Supplementary Table 1. Collapsing models and statistical results of *PHGDH* variants in each model.

	Model 1a Ultra Rare Polyphen	Model 1b Ultra Rare REVEL	Model 2a Very Rare Polyphen	Model 2b Very Rare REVEL	Model 3a Rare Polyphen	Model 3b Rare REVEL
gnomAD AF	0	0	0.00005	0.00005	0.001	0.001
Qualified PHGDH variants						
MacTel (793)	3	5	12	14	22	25
control (17610)	9	13	33	37	87	98
Odds Ratio	7.5	8.6	8.2	8.5	5.8	5.8
FET P	1.3×10^{-2}	7.9×10^{-4}	2.9×10^{-7}	2.0×10^{-8}	1.2×10^{-9}	7.5×10^{-11}

Odds Ratio and FET P (p-value obtained by the Fisher's Exact Test) are determined from the numbers of qualified variants, either PolyPhen as "probably pathogenic" or REVEL >0.5, in each model that included all classes of variants (missense, nonsense, indel, splicing-affecting, etc.).

Supplementary Table 2. Selected candidate genes for association with MacTel based on functional role in sphingolipid and/or serine metabolism pathways

Gene	Name	Collapsing FET P	Collapsing OR	Collapsing Model	Collapsing Rank	Selection Criteria
SGPP2	sphingosine-1-phosphate phosphatase 2	0.0026	4.2	3a	46	SPH
ALDH1A1	aldehyde dehydrogenase 1 family member A1	0.0038	13.4	1b	22	SPH
CERS1	ceramide synthase 1	0.0045	5.3	2b	29	SPH Serine
GAL3ST2	galactose-3-O-sulfotransferase 2	0.0110	2.5	3a	159	SPH
DGAT1	diacylglycerol O-acyltransferase 1	0.0218	2.9	2a	131	SPH
SMPD3	sphingomyelin phosphodiesterase 3	0.0218	2.9	3b	198	SPH Serine
CBS	cystathionine-beta-synthase	0.0246	5.6	1a	112	Serine
FAM57B	family with sequence similarity 57 member B	0.0248	11.0	1a	141	SPH
ENPP6	ectonucleotide pyrophosphatase/phosphodiesterase 6	0.0258	2.8	2b	146	SPH
ST8SIA5	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 5	0.0280	2.8	3a	391	SPH
SLC27A4	solute carrier family 27 member 4	0.0280	2.8	3b	260	SPH
KDSR	3-ketodihydrosphingosine reductase	0.0328	2.7	3b	289	SPH Serine
NPC1L1	NPC1 like intracellular cholesterol transporter 1	0.0398	2.9	1a	215	SPH
ELOVL5	ELOVL fatty acid elongase 5	0.0433	2.8	3a	592	SPH
SGPP2	sphingosine-1-phosphate phosphatase 2	0.0473	3.1	2a	345	SPH
SPNS1	sphingolipid transporter 1 (putative)	0.0479	2.2	3a	665	SPH

Variants with PolyPhen predicted to be “possibly pathogenic” or REVEL>0.5 were considered as “qualified“ for collapsing analyses. Selections are based on FET P<0.05 in at least one of six collapsing models and association with sphingosine metabolism (SPH), or serine metabolism (Serine). See Supplementary Table 1 for collapsing models.

Supplementary Table 3. Relative gene expression between human cadaveric Retina and RPE. Positive Log2FoldChange values represent elevated expression in the Retina. Raw data from Cherry, T.J. et al. 2020 PNAS[1]

Gene	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
RPE65	1480.31	-5.62	0.70	-8.00	1.29E-15	1.98E-14
RHO	13708.80	4.36	0.46	9.44	3.57E-21	8.88E-20
PHGDH	42.32	-2.72	0.39	-6.95	3.63E-12	3.94E-11
PSPH	36.75	-0.27	0.40	-0.68	0.50	0.60
PSAT1	38.92	-2.01	0.53	-3.79	0.00015	0.00056
SHMT1	113.49	-1.48	0.28	-5.22	1.78E-07	1.06E-06
SHMT2	114.13	0.35	0.34	1.05	0.30	0.41
SPTLC1	394.66	0.03	0.22	0.13	0.89	0.92
SLC1A4	318.82	0.01	0.30	0.35	0.72	0.79
SLC1A5	38.19	-3.03	0.37	-8.19	2.64E-16	4.35E-15

Supplementary Table 4. HSAN1 patient cohort

Family and Patient #	MacTel Status	Relationship	Birth Year	gender	ethnicity	WES
HSAN1 patient I	MacTel/HSAN1	proband	1994	M	Caucasian	Y
HSAN1 patient II	MacTel/HSAN2	father	1965	M	Caucasian	Y
patient VII	non	NA	1949	M	Caucasian	
patient VIII	non	NA	1930	F	Caucasian	

Supplementary Table 5. Primers for qPCR

PSPH	Forward	GAGGACGCGGTGTCAGAAAT
	Reverse	GGTTGCTCTGCTATGAGTCTCT
SHMT1	Forward	CTGGCACAACCCCTCAAAGA
	Reverse	AGGCAATCAGCTCCAATCCAA
SHMT2	Forward	CCCTTCTGCAACCTCACGAC
	Reverse	TGAGCTTATAGGGCATAGACTCG
PHGDH	Forward	CTGCGGAAAGTGCTCATCAGT
	Reverse	TGGCAGAGCGAACAATAAGGC
PSAT1	Forward	TGCCGCACTCAGTGTTGTTAG
	Reverse	GCAATTCCCGCACAAGATTCT
ATF4	Forward	ATGACCGAAATGAGCTTCCTG
	Reverse	GCTGGAGAACCCATGAGGT
SLC1A4	Forward	TGTTTGCTCTGGTGTTAGGAGT
	Reverse	CGCCTCGTTGAGGGAATTGAA
SLC1A5	Forward	GAGCTGCTTATCCGCTTCTTC
	Reverse	GGGGCGTACCACATGATCC
36B4	Forward	GAAGCCACGCTGCTGAACAT
	Reverse	CAAGGCCAGGACTCGTTTGTA

Supplementary Table 6. Formulation of Custom KSR

	mg/L
L-Histidine	940
L-Isoleucine	3400
L-Methionine	90
L-Phenylalanine	1800
L-Proline	4000
L-Hydroxyproline	100
L-Threonine	2200
L-Tryptophan	440
L-Tyrosine	77
L-Valine	2400
Thiamine	33
Reduced glutathione	10
Ascorbic acid-2-PO4 (Mg Salt)	330
Transferrin (iron sat)	55
Insulin	100
Sodium selenite	0.07
AlbuMAX	83000
Trace elements B (1x) Corning cat# C866M55	
Trace elements C (1x) Corning cat# C866M56	

References

1. Cherry, T.J. *et al.* Mapping the cis-regulatory architecture of the human retina reveals noncoding genetic variation in disease. *Proc Natl Acad Sci U S A* **117**, 9001-9012 (2020).